UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/722,587	11/28/2003	Robert D. Rosenberg	P-6170-US	5678

49443 7590 12/08/2008

Pearl Cohen Zedek Latzer, LLP
1500 Broadway
12th Floor
New York, NY 10036

EXAMINER	
GOON, SCARLETT Y	

ART UNIT	PAPER NUMBER
1623	

MAIL DATE	DELIVERY MODE
12/08/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/722,587	ROSENBERG ET AL.	
	Examiner	Art Unit	
	SCARLETT GOON	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *5 November 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-65* is/are pending in the application.

4a) Of the above claim(s) *3-5,19,21,32-38,40,41,49-62,64 and 65* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,6-18,20,22-31,39,42-48 and 63* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-65* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *26 December 2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-65 are pending in the instant application.

Priority

This application claims priority to U.S. provisional application no. 60/429946 filed on 27 November 2002 and U.S. provisional application no. 60/456889 filed on 21 March 2003.

Information Disclosure Statement

The information disclosure statement (IDS) dated 26 December 2006 complies with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609, except where noted. Accordingly, it has been placed in the application file and the information therein has been considered as to the merits.

Reference J was not considered because a full citation which also includes the title of the article, was not included on the IDS.

Election/Restrictions

Applicant's election with traverse of Group I, claims 1-31, 39, 42-48 and 50-64, drawn to a method of preparing a sulfated polysaccharide capable of binding to a binding partner, in the reply filed on 5 November 2008 is acknowledged. Applicants further elect, with traverse, Pentasaccharide 15 as the single disclose compound.

Please note that the claims of Group II should be correctly classified in class 536, subclass 124, not in class 536, subclass 123.1, as indicated in the Office Action dated 17 September 2008.

The traversal is on the ground(s) that a search of the claims of Groups I-III and species do not pose a serious burden on the Examiner due to the relatedness of the claims at issue.

This is not found persuasive because, as indicated in the Office Action dated 17 September 2008, Group I and Group III are classified in different classes. Therefore, "the inventions have acquired a separate status in the art in view of their different classification".

The inventions of Group I and III are separate and distinct, related as product and process of making, as discussed in the Requirement for Restriction mailed 17 September 2008. See the Restriction Requirement page 2. As noted in MPEP § 806.05(f), the criteria for distinct inventions: (2) that the product as claimed can be made by another and materially different process. In the instant case, the compounds can be synthesized using a different synthetic route with different reagents.

Therefore, the inventions of Groups I and II are seen to be separate and distinct inventions properly restricted from each other.

Moreover, the search field for a composition is non-coextensive with the search field for a method of making the same compound. A reference to the compound herein would not necessarily be a reference to the method of making the compound herein under 35 USC § 103 because a search indicating the process or making a compound is

novel or unobvious would not extend to a holding that the product itself is novel or unobvious whereas a search indicating that the product is known or would have been obvious would not extend to a holding that the process or method is known or would have been obvious. Note that the search is not limited to patent files. Further, the search for the inventions of both Groups I and III would place an undue burden on the Office. Note regarding the classification of the inventions herein that the search is not limited to the patent files.

The inventions of Group I and II are unrelated, as discussed in the Requirement for Restriction mailed 17 September 2008. See the Restriction Requirement page 2. As noted in MPEP § 802.01 and § 806.06, the criteria for unrelated inventions are that they are not disclosed as capable of use together and they have different designs, modes of operation and effects. In the instant case, each method would result in a different outcome. A method of identifying a polysaccharide binding partner would not necessarily be related to a method of preparing a sulfated polysaccharide that is capable of binding to a binding partner because in detecting or identifying a polysaccharide binding partner, one would need to explore multiple binding partners to determine if it binds to the polysaccharide. Furthermore, Applicants are requested to noted that the recitation "capable of binding to a binding partner" is considered a property and intended use of the sulfated polysaccharide. Moreover, the outcomes would be different. A method of preparing a sulfated polysaccharide would result in a sulfated polysaccharide whereas a method of identifying a polysaccharide binding partner would not necessarily provide the same result, that of a sulfated polysaccharide.

Therefore, the inventions of Groups I and II are seen to be unrelated inventions properly restricted from each other.

Thus, an undue burden on the Office is seen for the search all inventions herein.

The requirement is still deemed proper and is therefore made FINAL.

Claims 32-38, 40, 41 and 49 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 5 November 2008.

Claims 3-5, 19, 21, 50-62, 64 and 65 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 5 November 2008.

Claims 1, 2, 6-18, 20, 22-31, 39, 42-48 and 63 will be examined on its merits herein.

Claim Objections

Claims 18, 20 and 22-31 objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend from any other multiple dependent claim. See MPEP § 608.01(n). It is noted that claims 3 and 4 have been withdrawn from consideration as being drawn to a nonelected species. However, this objection is made of record to draw Applicants' attention to the improper form of the claim.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).
A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.
Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 2, 6, 8, 10-13, 18, 20, 22-24 and 26-30 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 13, 18, 19, 24, 29 and 30 of copending application no. 11/204391.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application is drawn to a method for the preparation of N-sulfate derivatives of non-sulfated N-acetyl heparosan polysaccharides comprising the steps of (a) contacting a non-sulfated N-acetyl heparosan polysaccharide witn N-deacetylase-N-sulfotransferase and glucuronosyl C-5 epimerase to generate an iduronic acid-enriched polysaccharide; (b) contacting the product in (a) with 6-O-sulfotransferase and 3-O-sulfotransferase; and (c) isolating the product of (b) which yields N-deacetylated N-sulfate derivatives of non-sulfated N-acetyl heparosan (claims 13 and 24). The 3-O-sulfotransferase is 3-OST1, 3-OST2, 3-OST3, 3-OST4 or

3-OST5 (claims 18 and 29). The 6-O-sulfotransferase is 6-OST1, 6-OST2 or 6-OST3 (claims 19 and 30).

The claims of the instant application are drawn to a method of preparing a sulfated polysaccharide or heparan sulfate comprising treating an unsulfated or incompletely sulfated polysaccharide or unsulfated heparan synthon with at least one enzyme (claims 1, 2, 8 and 10). The enzyme is selected from the group consisting of an N-deacetylase, an N-sulfotransferase, an epimerase and an O-sulfotransferase (claim 6). The method comprises (a) treating an unsulfated polysaccharide with an N-deacetylating reagent; (b) treating the step (a) product with an N-sulfating reagent; (c) treating the step (b) product with an epimerizing reagent; and (d) treating the step (c) product with at least one O-sulfating reagent (claims 11 and 12). The heparan synthon is a non-sulfated N-acetyl heparosan (claim 13). The deacetylating reagent is selected from the group consisting of a deacetylase and N-deacetylase-N-sulfotransferase (claims 18 and 20). The epimerizing reagent is selected from the group consisting of C5-epimerase (claim 22). The O-sulfating reagent incorporates a 3-O-sulfate group or a 6-O-sulfate group (claims 23, 24 and 26). The O-sulfating reagent is a 3-O-sulfotransferase selected from the group consisting of 3-OST1, 3-OST2, 3-OST3, 3-OST4, 3-OST5 and 3-OST6 (claims 27 and 28). The O-sulfating reagent is a 6-O-sulfotransferase selected from the group consisting of 6-OST1, 6-OST2 and 6-OST3 (claims 29 and 30).

Thus, the instant claims 1, 2, 6, 8, 10-13, 18, 20, 22-24 and 26-30 are seen to be anticipated by claims 13, 18, 19, 24, 29 and 30 of copending application no. 11/204391.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1, 2, 6, 8, 10-18, 20 and 22-31 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 6, 16, 17, 19, 20, 23, 29, 39, 41, 42, 81, 85 and 88 of copending application no. 10/986058.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application is drawn to a method for the synthesis of an epimerically enriched form of a sulfated heparosan polysaccharide, comprising an acceptor heparosan polysaccharide with PAPS, at least one sulfotransferase, a p-nitrophenyl sulfate donor, an arylsulfatase and an epimerase (claims 1, 23 and 81). The epimerase is a glucuronosyl C5 epimerase (claims 6 and 29). The sulfated heparosan is isolated (claims 16). The sulfotransferase is an N-deacetylase-N-sulfotransferase, heparin sulfate 2-O-sulfotransferase, 6-O-sulfotransferase, 3-O-sulfotransferase, 2-O-sulfotransferase, or a combination thereof (claims 17 and 39). The 3-O-sulfotransferse is 3-OST1 (claims 19, 41 and 88). The 6-O-sulfotransferase is 6-OST1, 6-OST2 or 6-OST3 (claims 20, 42 and 85).

The claims of the instant application are drawn to a method of preparing a sulfated polysaccharide or heparan sulfate comprising treating an unsulfated or incompletely sulfated polysaccharide or unsulfated heparan synthon with at least one enzyme (claims 1, 2, 8 and 10). The enzyme is selected from the group consisting of

an N-deacetylase, an N-sulfotransferase, an epimerase and an O-sulfotransferase (claim 6). The method comprises (a) treating an unsulfated polysaccharide with an N-deacetylating reagent; (b) treating the step (a) product with an N-sulfating reagent; (c) treating the step (b) product with an epimerizing reagent; and (d) treating the step (c) product with at least one O-sulfating reagent (claims 11 and 12). The heparan synthon is a non-sulfated N-acetyl heparosan (claim 13). The unsulfated polysaccharide or heparan synthon is isolated from a cell or *E. coli* bacteria (claims 14-17). The deacetylating reagent is selected from the group consisting of a deacetylase and N-deacetylase-N-sulfotransferase (claims 18 and 20). The epimerizing reagent is selected from the group consisting of C5-epimerase (claim 22). The O-sulfating reagent incorporates a 2-O-sulfate group, 3-O-sulfate group or a 6-O-sulfate group (claims 23-26). The O-sulfating reagent is a 3-O-sulfotransferase selected from the group consisting of 3-OST1, 3-OST2, 3-OST3, 3-OST4, 3-OST5 and 3-OST6 (claims 27 and 28). The O-sulfating reagent is a 6-O-sulfotransferase selected from the group consisting of 6-OST1, 6-OST2 and 6-OST3 (claims 29 and 30). The O-sulfating reagent is a 2-O-sulfotransferase (claim 31).

Thus, the instant claims 1, 2, 6, 8, 10-18, 20 and 22-31 are seen to be anticipated by claims 1, 6, 16, 17, 19, 20, 23, 29, 39, 41, 42, 81, 85 and 88 of copending application no. 10/986058.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-31 and 39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation "incompletely sulfated polysaccharide" and "incompletely sulfated heparin sulfate" in claims 1 and 2, respectively, render claims 1-31 herein indefinite. One of ordinary skill in the art is aware that heparan can be sulfated by N-sulfation or O-sulfation at multiple sites to different degrees. N-sulfation occurs at the 2-position of the glucosamine residue while O-sulfation can occur at the 2- and/or 3-positions of iduronic/glucuronic acid and the 3- and/or 6-position of N-acetylglucosamine or N-sulfoglucosamine. Thus, in the absence of a clear definition in the Specification, it is unclear what constitutes incompletely sulfated since it is not necessary for sulfation to occur at all the possible sites.

The recitation "[a] method of synthesizing a selected from the group" in claim 39 renders the claim herein indefinite. It is unclear what the Applicants intend on synthesizing.

The use of brackets and/or bonds that are not attached to any atoms to denote Polysaccharide 1, Polysachcaride 2, Polysaccharide 3, Polysaccharide 4, Polysaccharide 5, Polysaccharide 6, Polysaccharide 7, Polysaccharide 8,

Polysaccharide 10 and Polysaccharide 11, in Figure 3, Figure 4, Figure 5, Figure 9 and Figure 20 renders claim 39 herein indefinite. It is unclear whether the bonds that are not attached to any atoms indicate that the structure is repeated or whether an atom was not drawn. Furthermore, the presence of brackets generally represent repeating units. However, this is unclear as the number of repeating units is not denoted next to the brackets, as is typically the case.

Claims 7 and 9 recites the limitation "chemical reagents" in line 2. There is insufficient antecedent basis for this limitation in the claim since the methods of claims 1 or 2 do not include chemical reagents. Furthermore, Applicants are requested to note that the chemical reagents would read on the non-elected species.

Claim 44 recites the limitation "nitrous acid and sodium borohydride" in line 5. There is insufficient antecedent basis for this limitation in the claim since the method of claim 1 does not include chemical reagents. Furthermore, Applicants are requested to note that the chemical reagents would read on the non-elected species.

Claim 39 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are those steps required for the synthesis of the indicated compounds. Additionally, the claims recite specific polysaccharides, the structures of which are not shown in the claims. It is noted that the structures are indicated in the Drawings of the Specification. To further clarify what is claimed, it is respectfully suggested that Applicants include the structure for the claimed compounds in the instant claims.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 42 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 42 recites "[a] method of 2-O-sulfating Polysaccharide 10, comprising the steps of treating Polysaccharide 10 with epimerase and 2-OST1". The Specification only discloses a method of 2-O-sulfating Polysaccharide 11 in Figure 20 and Example 20. Thus, the method of 2-O-sulfating Polysaccharide 10 as instantly claimed, is not adequately described in the Specification.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 11-13, 18, 20 and 22-31 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The method of preparing a sulfated polysaccharide and/or heparin sulfate comprising the steps as claimed have the same characteristics as found naturally and therefore do not constitute statutory

subject matter. In the absence of the hand of man, the natural process for the biosynthesis of heparin sulfate is considered non-statutory subject matter.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Section [0001]

Claims 1, 2, 6-10 and 13-17 are rejected under 35 U.S.C. 102(b) as being anticipated by journal publication by Wei *et al.* (PTO-892, page 1, Ref. U).

Wei *et al.* disclose that the biosynthesis of heparin sulfate utilizes a single protein that possesses both N-deacetylase and N-sulfotransferase activities (abstract). Towards characterizing the activity of the N-deacetylase, the release of [^{3}H]acetate from N-[^{3}H]acetylated polysaccharide derived from *Escherichia coli* K5 was measured (p. 3886, column 1, first paragraph).

It is noted that Wei *et al.* do not disclose the amount of sulfates present in the *Escherichia coli* K5 polysaccharide. However, as evidenced by Vann *et al.* (PTO-892, page 1, Ref. V), the capsular polysaccharide from *Escherichia coli* 010:K5:H4 is a repeating disaccharide unit comprising 4-β-glucuronyl-1,4-α-N-acetylglucosaminyl residues (abstract) that is similar to that of desulfo-heparin (p. 363, column 1,

paragraphs 2 and 3). Wei *et al.* indicates that heparan sulfate and heparin only differ in sulfate content and iduronic acid content (p. 3888, column 1, first full paragraph).

Thus, the assay used in characterizing N-deacetylase activity, wherein an acetate residue is removed from the N-acetylated polysaccharide of *Escherichia coli* K5, anticipates the method of preparing a sulfated polysaccharide in claims 1, 2, 6-10 and 13-17.

Section [0002]

Claims 1, 2, 6-13, 18, 20, 22-31, 46 and 47 are rejected under 35 U.S.C. 102(b) as being anticipated by journal publication by Perrimon *et al.* (PTO-892, page 1, Ref. W).

Perrimon *et al.* disclose the biosynthesis of heparan sulfate chains. After the common tetrasaccharide linkage region is formed on the core protein, it is further modified by the addition of alternating GlcA and GlcNAc residues catalyzed by heparan sulfate polymerase (p. 725, column 2, first incomplete paragraph). Once the chain is assembled, the individual saccharide units undergo a number of sequential modifications by various Golgi enzymes: N-deacetylase/N-sulfotransferse (NDST), uronosyl C5-epimerse, 2-O-sulfotransferase (2-OST), 6-O-sulfotransferase (6-OST) and 3-O-sulfotransferase (3-OST) (p. 725, column 2, last incomplete paragraph). The enzymes do not modify all the available sugars in the chain, which results in extensive sequence diversity in the final chain (p. 725-726, bridging paragraph). A schematic of the process is shown in Figure 1, (p. 725, column 2). The enzymes that participate in

heparan sulfate biosynthesis have been identified on the molecular level and are indicated in Table 1 (p. 726, column 2). These enzymes include 2-OST1, 3-OST1, 3-OST2, 3-OST3, 6-OST1, 6-OST2, 6-OST3, 6-OST4, 6-OST5, 6-OST6 and 6-OST7.

It is noted that Perrimon *et al.* do not explicitly disclose whether 2-O-sulfates, 3-O-sulfates and/or 6-O-sulfates are incorporated into the polysaccharide. However, as Perrimon *et al.* do disclose that the enzymes result in extensive diversity of the chain and these chains are modified by a 2-O-sulfotransferase, a 6-O-sulfotransferase (6-OST) and a 3-O-sulfotransferase, then it is the Office's position that 2-O-sulfates, 3-O-sulfates and/or 6-O-sulfates are incorporated into the polysaccharide.

With regards to the method wherein 2-O-sulfation occurs after the epimerization step, it is evidenced by Kobayashi *et al.* (PTO-892, page 1, Ref. X, abstract) that heparan sulfate 2-O-sulfotransferase catalyzes the transfer of sulfate from adenosine 3'-phosphate 5'-phosphosulfate only to position 2 of an iduronic acid residue of heparan sulfate. Therefore, 2-O-sulfation by a 2-O-sulfotransferase necessarily occurs after epimerization.

Thus, the biosynthesis of heparin sulfate, disclosed by Perrimon *et al.*, anticipates claims 1, 2, 6-18, 20, 22-31, 46 and 47.

Section [0003]

Claim 39 is rejected under 35 U.S.C. 102(b) as being anticipated by journal publication by Kusche *et al.* (PTO-892, page 2, Ref. U).

Kusche *et al.* disclose the ability of solubilized mastocytoma microsomes to sulfate four nonsulfated pentasaccharides of the general structure GlcN-GlcA/IdoA-GlcN-GlcA/IdoA-GlcN in the presence of [^{35}S]PAPS. The nonsulfated pentasaccharides are shown in Table I, denoted as compounds I-G, I-I, G-I and G-G (p. 7402, column 1). Analysis of the products of the [^{35}S]sulfate transfer to the nonsulfated pentasaccharides revealed that all of the inorganic [^{35}S]sulfate had been incorporated as N-[^{35}S]sulfate (p. 7402, column 2, first full paragraph). Sulfation of pentasaccharide G-I results in instantly claimed method of synthesizing Polysaccharide 2.

Thus, the sulfation of pentsaccharide G-I at the N-position by incubation of the pentasaccharides with solubilized mastocytoma microsomes and [^{35}S]PAPS, disclosed by Kusche *et al.*, anticipates claim 39.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Section [0004]

Claim 42 is rejected under 35 U.S.C. 103(a) as being unpatentable over journal publication by Perrimon *et al.* (PTO-892, page 1, Ref. W).

The teachings of Perrimon *et al.* were as described above in section [0002] of the claim rejections under 35 USC § 102.

Perrimon *et al.* do not explicitly teach that the instantly claimed method is used to modify Polysaccharide 10 with a 2-O-sulfate group.

However, Perrimon *et al.* do teach that the initially assembled heparin sulfate chain, before any modification, consists of alternating GlcNAc/GlcA residues, followed by the introduction of N-sulfate groups by N-deacetylase/N-sulfotransferase. It is this structure that Applicants are claiming is modified with a 2-O-sulfate. Therefore, as Perrimon *et al.* further teach that the enzymes do not modify all the available sugars in

the chain, it is likely that some portion of the resulting chain is not modified with 6-O-sulfates or 3-O-sulfates, and thus has the same structure as Polysaccharide 10. Perrimon *et al.* then teach that the N-sulfated polysaccharide is further modified by a GlcA C-5 epimerase and O-sulfotransferase. Once again, the enzymes do not modify all the available sugars in the chain. Therefore, since heparan sulfate 2-O-sulfotransferase catalyzes the transfer of sulfate from adenosine 3'-phosphate 5'-phosphosulfate only to position 2 of an iduronic acid residue of heparan sulfate (as evidenced by Kobayashi *et al.*, PTO-892, Ref. X, abstract), it is *prima facie* obvious that this modification would result in some portion of the heparan sulfate chain that has the instantly claimed Polysaccharide 10 structure modified with an epimerase and 2-O-sulfate residue.

Thus, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art.

Section [0005]

Claims 43 and 45 are rejected under 35 U.S.C. 103(a) as being unpatentable over journal publication by Perrimon *et al.* (PTO-892, page 1, Ref. W) as applied to claims 1, 2, 6-13, 18, 20, 22-31, 46 and 47, further in view of journal publication by Kushe *et al.* (PTO-892, page 2, Ref. U), in view of journal publication by Nader *et al.* (PTO-892, page 2, Ref. V) and journal publication by Myette *et al.* (PTO-892, page 2, Ref. W), in view of journal publication by Bick *et al.* (PTO-892, page 2, Ref. X).

The teachings of Perrimon *et al.* were as described above in section [0002] of the claim rejections under 35 USC § 102.

Perrimon *et al.* do not explicitly teach the instantly claimed method, which also includes the steps of a heparitinase and a $\Delta^{4,5}$ glycuronidase.

Kusche *et al.* teach the various substituents of heparin that are important for antithrombin binding. The antithrombin-binding region in heparin is shown in Figure 1 (p. 7401, column 1). As indicated, the 3-O-sulfate group of unit III is essential for the high affinity binding of heparin to antithrombin and is a marker component of the antithrombin-binding region (Fig. 1 legend). The 6-O-sulfate group of unit I and the N-sulfate groups of units III and V are also critically important for antithrombin binding. The modification of the amino group of unit I with either an acetate or sulfate group does not affect antithrombin binding. Additionally, the sulfate groups at C-2 and C-6 of units IV and V, respectively, are less essential for antithrombin binding.

Nader *et al.* teach the purification and substrate specificity of heparitinase I and heparitinase II from *Flavobacterium heparinum*. Heparitinase I acts on N-acetylated or N-sulfated glucosaminido-glucuronic acid linkages of heparan sulfate (abstract). Heparitinase II acts upon heparan sulfate producing disulfated, N-sulfated and N-acetylated-6-sulfated disaccharides, and small amounts of N-acetylated disaccharide (abstract).

Myette *et al.* teach the cloning and substrate specificity of the heparin/heparan sulfate $\Delta^{4,5}$ unsaturated glycuronidase from *Flavobacterium heparinum*. This enzyme hydrolyzes the unsaturated $\Delta^{4,5}$ uronic acid at the nonreducing end of oligosaccharides

that result from prior heparinase eliminative cleavage (abstract). It discriminates both on the basis of glycosidic linkage and sulfation pattern (abstract).

Bick *et al.* teach that low molecular weight heparins (LMWHs), each of which is an inhibitor of the coagulation process, have differential biochemical and pharmacological behavior with respect to their anti-Xa and anti-IIa binding (abstract). This is primarily due to the composition of each product manufactured by different patented methods. Thus, of the different available LMWHs, enoxaparin, dalteparin and ardeparin have been approved for DVT prophylaxis, but only enoxaparin and dalteparin have been approved for acute coronary syndrome. Bick *et al.* further teach that even at optimized dosages, the clinical profile of each drug may be different.

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Perrimon *et al.*, concerning the biosynthesis of heparan sulfate chains, with the teachings of Kusche *et al.*, regarding the importance of certain substituents of heparin for antithrombin binding, with the teachings of Nader *et al.*, regarding the specificity of heparitinase I and heparitinase II, with the teachings of Myette *et al.*, the cloning and substrate specificity of the heparin/heparan sulfate $\Delta^{4,5}$ unsaturated glycuronidase, with the teachings of Bick *et al.*, regarding the differential biochemical and pharmacological behavior of differently manufactured low molecular weight heparins. One would have been motivated to modify the synthesis of heparin sulfate as described by Perrimon *et al.*, with heparin degrading enzymes, such as those taught by Nader *et al.* and Myette *et al.*, while bearing in mind the important residues for antithrombin-binding, as taught by Kusche *et al.*, so as to obtain a heparin with

biochemical and pharmacological properties that permit its use in a variety of applications as an anti-coagulant, as compared to the limited applicable use of the LMWHs as described by Bick *et al.*

Thus, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art.

Section [0006]

Claim 48 is rejected under 35 U.S.C. 103(a) as being unpatentable over journal publication by Perrimon *et al.* (PTO-892, page 1, Ref. W) as applied to claims 1, 2, 6-13, 18, 20, 22-31, 46 and 47, further in view of journal publication by Kovensky *et al.* (PTO-892, page 3, Ref. U).

The teachings of Perrimon *et al.* were as described above in section [0002] of the claim rejections under 35 USC § 102.

Perrimon *et al.* do not explicitly teach a method wherein the product of step (a) is treated with a 2-O-sulfating reagent.

Kovensky *et al.* teach the chemical modification of glycosaminoglycans by selective 2-O-sulfation of glucuronic acid residues in heparan sulfate. It has been shown sulfation of heparan sulfates improve their anticoagulant activity, though little or no structural characterization of the products can be found in the literature (p. 120, column 1, first paragraph). Sulfation of glucuronic acid residues may allow for the study of the biological activity of these sulfated compounds which have been suggested to be involved in the control of cell growth, and further allow the elucidation of their actual

functional role (p. 120, column 1, first paragraph). HSII is a heparin sulfate composed mainly of glucuronic acid residues. This polymer was chemically sulfated to give selectively 2-O-sulfated glucuronic acid residues (p. 120, column 2, first full paragraph).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Perrimon *et al.*, concerning the biosynthesis of heparan sulfate chains, with the teachings of Kovensky *et al.*, regarding the chemical modification of glycosaminoglycans by selective 2-O-sulfation of glucuronic acid residues in heparan sulfate. As suggested by Kovensky *et al.*, one would have been motivated to combine the teachings so as to study the biological activity of these sulfated compounds which have been suggested to be involved in the control of cell growth, and further allow the elucidation of their actual functional role (p. 120, column 1, first paragraph).

Thus, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art.

Section [0007]

Claim 63 is rejected under 35 U.S.C. 103(a) as being unpatentable over journal publication by Kusche *et al.* (PTO-892, page 2, Ref. U).

Kusche *et al.* teach the ability of solubilized mastocytoma microsomes to sulfate four nonsulfated pentasaccharides of the general structure GlcN-GlcA/IdoA-GlcN-glcA/IdoA-GlcN, and their N-sulfated derivatives, in the presence of [^{35}S]PAPS. The nonsulfated and N-sulfated pentasaccharides are shown in Table I (p. 7402, column 1).

Analysis of the products of the [^{35}S]sulfate transfer to the nonsulfated pentasaccharides revealed that all of the inorganic [^{35}S]sulfate had been incorporated as N-[^{35}S]sulfate (p. 7402, column 2, first full paragraph). Analysis of the products of the [^{35}S]sulfate transfer to the sulfated pentasaccharides suggested occurrence of O-[^{35}S]sulfate groups at both the c-6 of the nonreducing terminal glucosamine unit and C-3 of the internal glucosamine unit (abstract). Additionally, these products had high affinity for antithrombin (abstract). The antithrombin-binding region in heparin is shown in Figure 1 (p. 7401, column 1). As indicated, the 3-O-sulfate group of unit III is essential for the high affinity binding of heparin to antithrombin and is a marker component of the antithrombin-binding region (Fig. 1 legend). The 6-O-sulfate group of unit I and the N-sulfate groups of units III and V are also critically important for antithrombin binding. The modification of the amino group of unit I with either an acetate or sulfate group does not affect antithrombin binding. Additionally, the sulfate groups at C-2 and C-6 of units IV and V, respectively, are less essential for antithrombin binding. Extensive studies of the biosynthesis of heparin and heparan sulfate in a cell-free microsomal preparation from a mouse mastocytoma have delineated the biosynthetic sequence of events (p. 7401, column 1, first incomplete paragraph). In the presence of both UDP-GlcNAc and UDP-GlcA, a nonsulfated polysaccharide ((GlcA-GlcNAc)$_n$) is formed that is covalently linked to a protein core in a proteoglycan structure. Upon addition of the sulfate donor PAPS, a series of modifications take place, beginning with deacetylation and N-sulfation of the GlcNAc units. The latter reaction creates the proper substrate structure for C-5 epimerization of GlcA to IdoA units, and the assembly process is concluded by stepwise

O-sulfation in several positions (C-2 of IdoA and C-2 or C-3 of GlcA units, C-3 and C-6 of GlcN units).

It is noted that Kusche *et al.* do not teach a method of producing Pentasaccharide 15 as instantly claimed, by 3-O-sulfating Pentasaccharide 14. However, Kusche *et al.* do provide a base non-sulfated pentasaccharide (compound G-I of Table I) for heparin synthesis and further teach the biosynthetic steps of heparin and heparan sulfate biosynthesis (p. 7401, column 1, first incomplete paragraph). Kusche *et al.* further teach that a compound similar to Pentasaccharide 15, that which is shown in Figure 1, with the exception of the sulfate group at C-6 of unit V, is the structure of the antithrombin-binding region in heparin and that the presence of a sulfate group at C-6 of unit V is not essential for binding. Thus, it would have been *prima facie* obvious for one of ordinary skill in the art to modify the non-sulfated pentasaccharide to produce a sulfated compound that is capable of binding to the antithrombin-binding region, as indicated by Kushe *et al*. One would have been motivated to prepare such an antithrombin-binding compound due to its important function as a blood anticoagulant (abstract).

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SCARLETT GOON whose telephone number is 571-

270-5241. The examiner can normally be reached on Mon - Thu 7:00 am - 4 pm and every other Fri 7:00 am - 12 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Shaojia Anna Jiang/
Supervisory Patent Examiner, Art Unit 1623

/SCARLETT GOON/
Examiner
Art Unit 1623